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Comparison of propofol-based versus volatile-based anaesthesia and postoperative sedation in cardiac surgical patients: a prospective, randomized, study

Marcin Wąsowicz[1, 2], Angela Jerath[1, 2], Warren Luksun[1, 2], Vivek Sharma[1, 2], Nicholas Mitsakakis[3], Massimiliano Meineri[1, 2], Rita Katznelson[1, 2], Terrence Yau[4] , Vivek Rao[4], William Scott Beattie[1, 2]

[1]Department of Anesthesia and Pain Management, Toronto General Hospital/University Health Network, Toronto, Canada
[2]Department of Anesthesia, University of Toronto, Toronto, Canada
[3]Institute for Health Policy, Management and Evaluation, University of Toronto and Biostatistics Research Unit, University Health Network, Toronto, Canada
[4]Division of Cardiac Surgery, Peter Munk Cardiac Centre, University Health Network and Department of Surgery, University of Toronto, Toronto, Canada

Abstract

Background: Clinical trials have shown conflicting results regarding the use of volatile anaesthesia before or after an ischaemic insult in cardiac surgical patients and its effect on myocardial injury. This may be attributable to the failure of continuing volatile agents into the early postoperative period. We hypothesised that combined volatile-based anaesthesia and postoperative sedation would decrease the extent of myocardial injury after coronary artery bypass grafting (CABG) when compared with an intravenous, propofol-based approach. This study aimed to assess the feasibility of the perioperative protocol and investigate whether volatile anaesthesia provides cardioprotection in patients undergoing CABG.
Methods: Randomized, controlled trial enrolling 157 patients with preserved left ventricular function scheduled for elective or urgent on-pump CABG. Patients received either volatile- or propofol-based anaesthesia and postoperative sedation. Volatile sedation in the ICU was provided with the use of the AnaConDa® device (Sedana Medical, Uppsala, Sweden). The primary outcome was myocardial injury measured by serial troponin measurement at the beginning of surgery, 2, 4 and 12–16 h after ICU admission. The secondary outcome was cardiac performance expressed as cardiac index (CI) and the need for inotropic and vasopressor drug support. The peak postoperative troponin level was defined as the highest level at any time in the first 16 h after surgery.
Results: 127 patients completed the study protocol, 60 patients in the volatile group and 67 patients in the propofol group. Troponin levels were similar between groups at all of the measured time points. There were no differences in cardiac index or vasoactive drug support except for the immediate post- cardiopulmonary bypass (CPB) period when patients in the volatile group had low systemic vascular resistance, high CI and required more vasopressors. There was no difference in postoperative kidney function, intensive care unit discharge or hospital discharge time.
Conclusions: The use of volatile-based anaesthesia and postoperative sedation did not confer any cardioprotection compared with propofol-based anaesthesia and sedation in patients who had good left ventricular function and were undergoing CABG.

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Key words: anaesthetics, volatile; anaesthetics, intravenous, propofol; pre-conditioning; post-conditioning; cardiac surgery

Clinical trial registration: Clinicaltrials.gov (NCT 01151254)

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Coronary artery bypass grafting (CABG) is frequently performed on patients with multi-vessel coronary disease [1], with almost 400,000 CABG procedures performed in North America in 2012 [1, 2]. Even though this number is slightly decreasing in favour of percutaneous coronary interventions, the overall CABG numbers remain in the same range [3, 4]. Currently, the mortality of elective CABG is generally below 2%, however on-pump CABG is associated with global myocardial ischaemia and corresponding postoperative myocardial biomarker (i.e., troponin) release [5]. The release of this easily measured biomarker provides a feasible clinical method to study perioperative strategies that may reduce myocardial injury.

It is has been over 20 years since Kersten *et al.* [6] published a landmark study demonstrating that the administration of isoflurane to experimental animals (dogs) prior to an ischaemic insult (occlusion of the left anterior descending coronary artery) after chest opening decreased the size of myocardial infarction. Since then, multiple experimental studies have shown that the use of volatile anaesthetics before an ischaemic insult can reduce myocardial damage [7]. Other studies have suggested that the use of volatile agents after ischaemia can provide further benefits through a post-conditioning effect [5]. However, the clinical efficacy of volatile anaesthesia in myocardial protection remains controversial, with 5 meta-analyses of studies on the effects of volatile anaesthesia in cardiac surgical patients on postoperative outcomes producing conflicting results [8–12]. Several of these studies have suggested that combining volatile-based pre- and post-conditioning may yield even better results.

The aim of the present study was to investigate perioperative outcomes in patients undergoing CABG surgery when combined anaesthesia and sedation was provided with either a volatile or intravenous (propofol) agent. We hypothesized that the combined application of volatile-based anaesthesia and postoperative sedation would result in better cardioprotection (measured by less troponin leak) [13, 14] and improved haemodynamics (measured by cardiac index and inotropic/vasopressor drug requirement).

METHODS

Approval of the study protocol was obtained in August 2009 from our institutional Research Ethics Board, while this study was registered at Clinicaltrials.gov (NCT 01151254). All patients enrolled in the trial provided written informed consent.

Patients screened for eligibility to participate in the study were scheduled for elective or urgent CABG with use of cardiopulmonary bypass (CPB). The inclusion criteria included patients scheduled for elective or urgent CABG with preserved ventricular function (ejection fraction > 40%). Exclusion criteria included a history of malignant hyperthermia or propofol infusion syndrome, emergency surgery (patients in cardiogenic shock or ongoing ischaemia), history of severe kidney disease (glomerular filtration rate below 30 mL min^{-1}) or severe liver disease (bilurubin > 2 mg dL^{-1}) and poorly controlled diabetes (glycosylated haemoglobin > 9%).

Patients were randomized 1:1 by a computer sequence block generator to receive either volatile-based anaesthesia and post-operative sedation, which we have labelled as the volatile group or total intravenous propofol-based anaesthesia, and postoperative **s**edation labelled as the propofol group.

All other anaesthetic and surgical procedures were standardized as described below. Volatile-based sedation within the ICU was provided via the AnaConDa® (Anaesthetic Conserving Device, Sedana Medical, Uppsala, Sweden). Approval for the postoperative volatile delivery device (AnaConDa®) was obtained from Health Canada, since at the time of commencing the study, this device was not registered for use in Canada. A pilot study to determine whether there was any volatile anaesthetic contamination into the Intensive Care Unit (ICU) ambient room was carried out prior to the current trial [15].

PREOPERATIVE, INTRAOPERATIVE AND POSTOPERATIVE MANAGEMENT

Apart from the choice of the anaesthetic agent (volatile anaesthetic or propofol), all other procedures were standardized. All patients received premedication with 1–2 mg of lorazepam applied sublingually 1 h prior to the procedure. Standard anaesthesia and monitoring devices including peripheral venous, arterial access was acquired under local anaesthesia (1% lidocaine). Then each patient received 0.05 mg kg^{-1} midazolam and was pre-oxygenated with 100% O_2 for 3 min. The induction of general anaesthesia consisted of fentanyl 5 mg kg^{-1} and with propofol 0.4–2 mg kg^{-1} until the loss of eyelash reflex. To facilitate tracheal intubation, patients received either rocuronium bromide 0.6 mg kg^{-1} or pancuronium 0.1 mg kg^{-1}. Central venous and pulmonary artery catheters (PAC) were inserted after the induction of general anaesthesia. The total dose of fentanyl given during anaesthesia did not exceed 5 mg kg^{-1}. During the re-warming phase of CPB, each patient received 1–2 mg of midazolam and an additional dose of rocuronium or pancuronium (20 or 2 mg, respectively). After the induction of general anaesthesia each patient in the volatile group received 0.6–2 MAC of either isoflurane or sevoflurane. The intraoperative dosing of the volatile agent was guided by the use of a bispectral index monitor (Aspect Medical System, MA, USA) aiming at BIS values between 40–60. Volatile anaesthetic was administered during CPB with a vaporizer

integrated with the fresh gas flow circuit. Postoperative sedation was commenced with the use of the AnaConDa® filled with the same volatile anaesthetic, which was used intraoperatively. It was continued until the patient was ready for extubation.

In the propofol group, after the induction of general anaesthesia, a maintenance infusion of propofol (2–6 mg kg^{-1} h^{-1}) was used. The depth of anaesthesia was similarly adjusted according to a bispectral index monitor (Aspect Medical System, MA, USA) aiming at BIS values between 40–60 and a diminished haemodynamic response. The same range of propofol doses was administered during CPB and after separation from CPB until leaving the operating room, where it was reduced to 0.5–2 mg kg^{-1} h^{-1} for postoperative sedation.

The dosing of the anaesthetic agent (volatile or propofol) used for postoperative sedation was based on the Richmond Sedation Agitation Score (RASS) [16]. Sedation was continued until the patient was ready for extubation. Patients were extubated once they achieved satisfactory haemodynamic stability, haemostasis, normothermia, cognitive function and successful completion of a spontaneous breathing trial, all of which was performed according to a standardized protocol [15]. Postoperative pain control consisted of morphine, paracetamol and oxycodone and followed standard protocols already implemented in the unit.

SURGICAL AND CARDIOPULMONARY BYPASS (CPB) MANAGEMENT

Anticoagulation during CPB was achieved with intravenous heparin (400 U kg^{-1} bolus with additional increments as necessary) to maintain an activated clotting time (ACT) above 480 seconds. The CPB circuit was primed with 1.5–1.8 L of Ringer's Lactate, 25 g of mannitol, 2,000–5,000 units of heparin, and 50 mEq of sodium bicarbonate. While conducting the study, the CPB circuit was equipped with a microporous polypropylene hollow-fibre oxygenator (Medtronic, St. Paul MN, USA). Management of CPB included retrograde autologous priming of the circuit whenever possible, alpha-stat pH management, a targeted mean perfusion pressure between 60–70 mm Hg, and pump flow rates of 2.0–2.5 L min^{-1} m^{-2}. Systemic temperatures were allowed to drift to 34° C. Myocardial protection was achieved with intermittent antegrade and, occasionally, retrograde blood cardioplegia. CPB circuits were not heparin-coated. During CPB, shed pericardial blood was salvaged into the cardiotomy suction reservoir and re-infused via the CPB circuit for as long as patients were anticoagulated. After separation from CPB, heparin was neutralised with protamine sulphate to a target ACT within 10% of the baseline (the initial dose was calculated based on the initial heparin dose and the protamine's neutralizing factor). All patients received a dose of antifibrinolytic drugs as previously described in detail [17].

The randomization schedule was created using a random number generator to create randomly permuted blocks of 8. The randomization schedule was concealed from the recruiters in sealed opaque envelopes stored in a locked cupboard in the trials office. After informed written consent was obtained, patients were allocated to groups on the day of surgery. A dedicated research coordinator performed recruitment and randomization to study intervention.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was myocardial injury measured as troponin leak. Troponin-I levels were measured using the Abbott Architect i2000 analyzer (Abbott Diagnostics Abbott Park Il) as previously described, where the upper reference limit is 0.07 μg L^{-1} [18]. Secondary outcomes are low cardiac output syndrome (cardiac index < 2.1 L m^{-2}), vasoactive drug support, laboratory renal and haematology values, incidence of postoperative arrhythmias, readiness and actual time for extubation, sedation scores, postoperative analgesia requirement, readiness of ICU and hospital discharge. Readiness for ICU discharge was clinically defined by the time at which the patient was extubated with stable cardio-respiratory and renal status. This was used because ICU discharge time is commonly delayed secondary to access to ward beds. Similarly, readiness for hospital discharge was used at the time when the patient no longer required acute medical or nursing care services. Postoperative analgesia requirements, extubation and sedation outcomes have been previously reported [19].

SAMPLE SIZE CALCULATION

Our initial sample size was estimated based on the assumption that in order to detect a decrease of the risk of low cardiac output by 30% (from current incidence in our institution of 28.6% to 20%) with power = 80% and an alpha = 0.05, each group needed to have 393 patients. A similar decrease of myocardial injury from a rate of 9.5% to 6.7% (based on internal data from hospital database) would require 1,434 patients in each group. Given the large sample sizes in the setting of introducing new technology for delivering volatile-based sedation in North America (AnaConDA®), we aimed to recruit a minimum 120 patients to assess specific safety and quality metrics such as atmospheric volatile levels, difficulties with the miniature vaporizer, and the quality of patient sedation. These have been reported previously [15, 19]. In addition, in a *post hoc* exploratory analysis, we also compared the proportion of patients in the two groups with peak troponin I levels greater than 50-fold over the upper reference limit (URL). The peak postoperative troponin level was defined as the highest level at any time in the first 24 hours after surgery. This is a good outcome as described by Domanski *et al.* [14] who demonstrated that a ratio of

peak troponin level to the normal URL beyond 50 was clearly associated with increase in 30 day mortality rates in cardiac surgical patients undergoing CABG. This becomes clinically significant at a 100-fold increase of URL [12, 13]. Therefore, troponin leak expressing myocardial injury is a clinically useful outcome as the URL can vary among institutions and cardiac output values are heavily influenced by differences in clinical practice and vasoactive drug use. To demonstrate a 20% reduction from a 50-fold increase in the URL at our laboratory (3.5 μg L^{-1}) using a 2 tailed t-test, a total sample size of 126 patients is required at 80% power, alpha 0.05 with a standard deviation of 1.4 μg L^{-1} [10, 12]. Thus, this study will provide the results on the degree of myocardial injury and cardiac performance measured as cardiac index and inotropic/vasopressor requirements.

STATISTICAL ANALYSIS

Continuous numerical variables were described with means and standard deviations (SD), while discrete variables were described with medians and interquartile ranges. Categorical data were described as frequencies and percentages. Numerical outcomes were compared between the two groups with the use of the Wilcoxon non-parametric test, while mean differences and confidence intervals (CI) were estimated. Categorical outcomes were compared using the Chi-square test, odds ratios (OR) and CI. Specifically, the primary outcome and continuous secondary outcomes were described with means and standard deviations (SD), while categorical secondary outcomes were described as frequencies and percentages. Primary outcomes and numerical secondary outcomes were compared between the two groups with the use of the Wilcoxon non-parametric test, while mean differences and confidence intervals were estimated. The Chi-square test was used for comparing categorical secondary outcomes.

The case report forms were verified and all data validated before the group allocation was revealed for the purposes of statistical analysis. All statistical analyses were carried out using R (R Core Team (2013) – R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) and SAS v 9.4 (Cary, NC, USA).

RESULTS

The study was conducted in accordance with the CONSORT guidelines [20, 21]. The patient study cohort and details describing flow are described in Figure 1. There were 127 CABG patients who completed the study protocol, with 67 receiving propofol and 60 receiving volatile anaesthesia and sedation (namely, 30 pts. received sevoflurane and 30 pts. received isoflurane). Of 157 patients who were randomized, we had to exclude 17 due to conversion to off-pump CABG. Thus, 140 patients were allocated to study intervention, while 13 patients had to be excluded, namely 11 in the volatile and 2 in propofol group, respectively. Patients' demographics are presented in Table 1. Patients in the volatile and propofol groups were similar with respect to left ventricular function and most co-morbidities. However, there were more patients suffering from diabetes mellitus and taking sulphonylurea medications as primary treatment for diabetes in the propofol group and more patients who had recent MI and suffered from CHF in the volatile group.

The degree of myocardial injury was assessed using troponin I levels. Baseline troponin levels were undetectable. Post-surgery, troponin levels increased significantly 2 h after ICU admission, peaked at 4 hours in the ICU and were starting to decline by 16 hours (Fig. 2). Although at all time points, troponin levels were slightly higher in the volatile group, the difference was not statistically significant. At two hours after ICU admission, troponin mean (SD) levels were 4.16 (4.14) μg L^{-1} for the volatile group and 3.47 (2.73) μg L^{-1} for the propofol group, with a mean difference of 0.69 (95% CI: -0.58–1.96, $P = 0.43$). At 4 hours post ICU admission, the troponin levels were 5.96 (5.60) μg L^{-1} for the volatile group and 5.21 (4.22) μg L^{-1} for the propofol group, with a mean difference of 0.75 (95% CI: -1.08–2.59, $P = 0.43$), while at 12–16 hours the values were 5.09 (5.02) μg L^{-1} for the volatile group and 5.07 (SD 6.81) μg L^{-1} for the propofol group, with a mean difference of 0.02 (95% CI: -2.12–2.16, $P = 0.66$).

In the exploratory *post hoc* analysis, 65% of the patients in the volatile group had peak troponin-I values larger than 50 times the URL, in comparison with 53.8% of the patients in the propofol group, giving an odds ratio estimate of 1.59 (95% CI: 0.78–3.30, $P = 0.21$). Similarly, the odds ratio of having a peak troponin I more than 100 times the URL was 1.18 (95% CI: 0.8–1.4) when compared with the baseline value.

Secondary outcomes are described in Tables 2 and 3. CI did not differ between the volatile and propofol groups when it was measured before sternotomy, with mean (SD) values of 2.16 (0.70) μg L^{-1} for the volatile group and 2.29 (1.13) μg L^{-1} for the propofol group, with a mean difference –0.13 (95% CI: -0.48, 0.22, $P = 0.48$); after CPB and chest closure, the values were 2.53 (0.52) μg L^{-1} in the volatile group and 2.65 (0.89) μg L^{-1} in the propofol group, with a mean difference -0.12 (95% CI: –0.39–0.14, $P = 0.35$); after extubation the values were 2.69 (0.56) μg L^{-1} in the volatile group and 2.60 (0.46) μg L^{-1} in the propofol group, with a mean difference = 0.10, 95% CI: –0.09, 0.28, $P = 0.32$); while before ICU discharge the values were 2.51 (0.36) μg L^{-1} for the volatile group and 2.54 (0.45) μg L^{-1} for the propofol group, with a mean difference of -0.03 (95% CI: -0.22–0.17, $P = 0.79$). The results of CI measurements are displayed in Supplemental

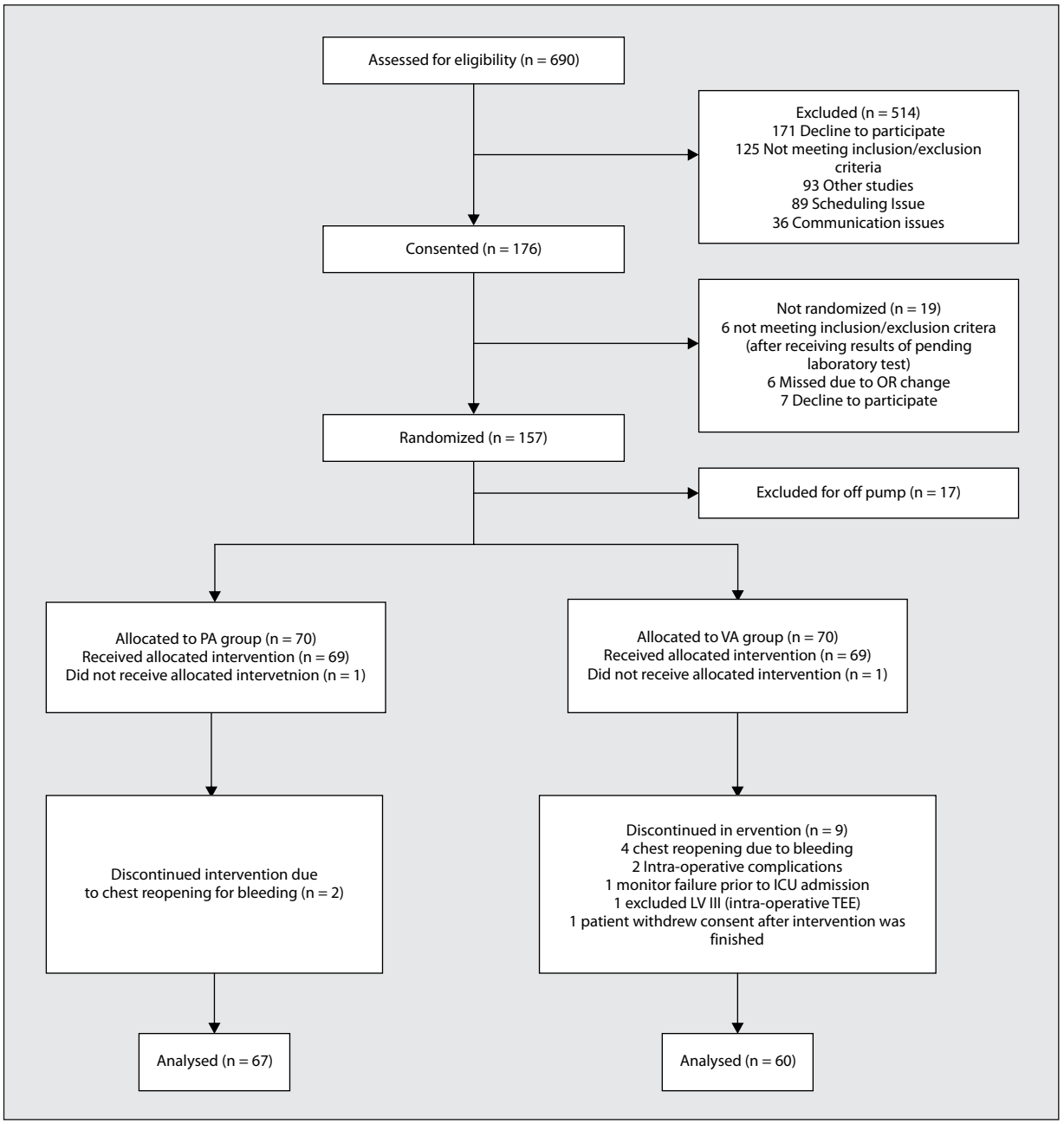

Figure 1. Flow chart demonstrating patients' enrolment according to CONSORT criteria. 690 patients scheduled for elective or urgent CABG were screened and, after exclusion of patients who did not meet inclusion criteria, declined to participate in the study or were already recruited to participate in different interventional study, we randomised 157 pts. Additional 17 pts had to be excluded due to conversion to off-pump CABG. Out of 140 pts, 127 fully completed the protocol and were analysed

Figure 3. The only significant difference in cardiac index measurements was after ICU admission. This was higher in the volatile group, 2.95 (0.71) μg L^{-1} versus 2.47 (0.42) μg L^{-1} the propofol group, with a mean difference of 0.48, (95% CI: 0.28–0.69, $P < 0.0001$). There was no difference in vasoactive drug support at any time point except for the immediate post-CPB period when vasopressor drug support was used more frequently. The incidence of atrial fibrillation and renal function was similar in both groups. Patients achieved faster readiness for extubation in the volatile group. However, there was no difference in overall ICU readiness for ward transfer and hospital discharge. Further results regarding extubation and sedation outcomes have been previously reported [19]. There were no deaths in this study.

DISCUSSION

The results of this study showed that combined volatile-based anaesthesia and postoperative sedation showed

Table 1. Pre-operative characteristics of patients who were randomised to propofol and volatile groups

Age, years	63 ± 10	65 ± 9
Male, n (%)	63 (94.0 %)	54 (90%)
Grade 1 LV*, n (%)	55 (74.3%)	50 (74.6%)
MI† < 30 days, n (%)	5 (7.5 %)	7 (10. %)
CHF‡, n (%)	0 (0%)	2 (3%)
COPD§, n (%)	5 (7.5 %)	3 (4.5%)
History of cerebrovascular disease, n (%)	8 (11.9 %)	5 (8.3 %)
Diabetes, n (%)	22 (33.3 %)	8 (13.3 %)
Sulphonylurea, n (%)	10 (14.9%)	4 (6.7 %)
Other diabetic, n (%)	4 (5.4%)	1 (1.5%)
eGFR (mL min^{-1} 1.73 m^{-2})	80.0 ± 20.5	80.4 ± 15.9
Preoperative aspirin	56 (84%)	55 (92%)
Preoperative cholesterol lowering agent (statin)	61 (91%)	53 (88%)
Preoperative Beta blocker	48 (72%)	49 (81%)

Abbreviations: *left ventricle, †myocardial infarction, ‡congestive heart failure, §chronic obstructive pulmonary disease, ll estimated glomerular filtration rate. Grade 1 LV-ejection fraction above 50%

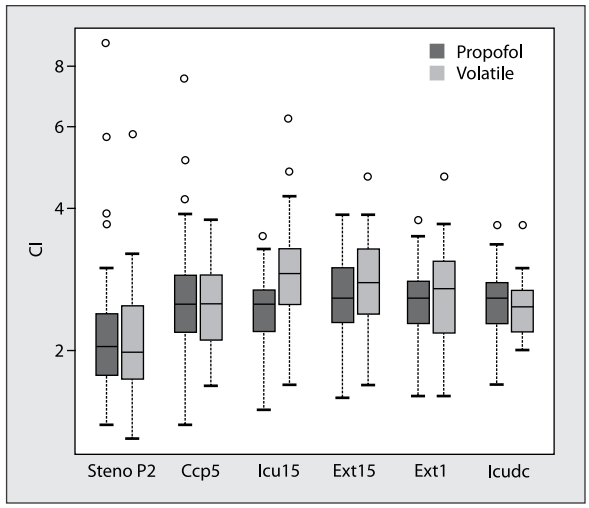

Figure 3. (Supplemental). Graphic presentation of serial measurements of cardiac output expressed as cardiac index. The only significant difference in cardiac index measurements was after ICU admission. It was higher in the volatile group, 2.95 (0.71) vs. 2.47 (0.42) in the propofol group, with a mean difference of 0.48, (95% CI: 0.28–0.69, $P < 0.0001$)

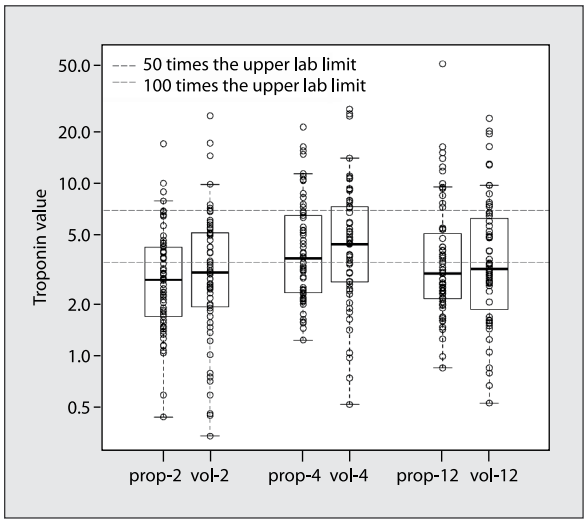

Figure 2. Graphic presentation of serial troponin measurements in volatile and propofol groups. Baseline troponin levels were undetectable. Post-surgery, troponin levels increased significantly 2 h after ICU admission, peaked at 4 hours in the ICU and were starting to decline by 16 hours. Although at all time points, troponin levels were slightly higher in the volatile group, the difference was not statistically significant. In the exploratory *post hoc* analysis, 65% of the patients in the volatile group had peak troponin-I values larger than 50 times the URL, in comparison with 53.8% of the patients in the propofol group, giving an odds ratio estimate of 1.59 (95% CI: 0.78–3.30, *P*-value = 0.21). Similarly, the odds ratio of having a peak troponin I more than 100 times the URL was 1.18 (95% CI: 0.8–1.4) when compared with the baseline value

no clinical or statistical difference in myocardial injury or haemodynamics in comparison with intravenous propofol. The only time point when CI was higher was in the volatile group and occurred on ICU admission; most likely due to the vasodilatatory effect of the volatile agent.

These results add to the ongoing debate regarding the merits of volatile-induced cardiac protection [7, 22]. There are multiple experimental and human studies, providing conflicting results regarding the role of volatiles for cardiac surgical patients. De Hert *et al.* published the first clinical study indicating that volatile exposure pre-CPB decreased troponin release after on-pump CABG surgery [5, 23]. However, several other studies, which applied volatiles pre- or post-CPB failed to show any clinically significant difference between volatile and intravenous anaesthesia and the extent of troponin release [24–27]. Flier *et al.* [24] randomized 100 cardiac surgery patients to volatile exposure pre-CPB with isoflurane or propofol and found no difference in troponin release. In a similar study, Hellström and colleagues randomized 100 on-pump CABG patients to volatile sedation in the ICU, only as a post-conditioning protocol, and found no difference in troponin T levels after 12 hours [25]. Soro *et al.* [26] randomized 75 patients to either sevoflurane or propofol anaesthesia and sedation and also found no difference in troponin I release. Finally, although Steurer *et al.* [27] randomized 117 on-pump cardiac patients to volatile or

Table 2. Intraoperative characteristics and surgical variables

Variables	Propofol (n = 67)	Volatile (n = 60)	*P*-value
Number of grafts	4 ± 1	4 ± 1	0.86
Cross clamp duration (min.)	72.1 ± 22.6	69.3 ± 24.2	0.67
Cardiac index –2 min. post-sternotomy (L min^{-1} m^{-2})	2.3 ± 1.1	2.2 ± 0.7	0.94
Cardiac index 510 mins post chest closure (L min^{-1} m^{-2})	2.7 ± 0.9	2.5 ± 0.5	0.16
SVI* 2 min. Post-sternotomy (mL m^{-2})	32.1 ± 9.5	33.2 ± 8.4	0.33
SVI* 5–10 mins post chest closure (mL m^{-2})	30.1 ± 9.5	30.0 ± 6.5	0.64
Inotropic support n (%)	26 (38.8%)	32 (53.3%)	0.11
Vasopressor, n (%)	12 (18.2%)	30 (50.0%)	< 0.001
RBC† transfusions (units)	0.53 ± 0.93	0.36 ± 0.87	0.12

Abbreviations: *stroke volume index, †red blood cells

Table 3. Postoperative variables

Variables	Propofol (n = 67)	Volatile (n = 60)	*P*-value
Cardiac index on ICU* admission (L min^{-1} m^{-2})	2.5 ± 0.4	2.9 ± 0.7	< 0.001
Cardiac index after extubation (L min^{-1} m^{-2})	2.6 ± 0.5	2.7 ± 0.6	0.31
Stroke volume index on ICU* admission (mL m^{-2})	28.4 ± 6.0	33.4 ± 7.4	< 0.001
Stroke volume 1 h after extubation (mL m^{-2})	28.1 ± 5.0	29.9 ± 7.0	0.27
Inotropic support, n (%)	29 (43.3%)	28 (46.7%)	0.84
Vasopressor use, n (%)	28 (37.8%)	31 (46.3%)	0.31
Atrial fibrillation on POD 1, n (%)	3 (4.1%)	7 (10.4%)	0.15
Hemoglobin on POD 1† (g L^{-1})	103.2 ± 13.4	103.7 ± 13.6	0.90
eGFR‡ on POD 1† (mL min^{-1} 1.73 m^{-2})	87.1 ± 21.7	82.7 ± 18.6	0.09
Hospital LOS (days)	6.8 ± 2.7	6.9 ± 3	0.71
Extubation Readiness Time (min)	219.6 ± 104.9	172.1 ± 175.5	< 0.001
ICU Discharge Readiness Time (min)	1662.9 ± 1882.7	1471.75 ± 1763.5	0.18

Abbreviations: *intensive care unit, †post-operative day 1, ‡estimated glomerular filtration rate

propofol ICU sedation and demonstrated a small decrease in troponin I levels, there was no translation in to larger clinical benefits such as a reduced length of ICU stay.

To summarize the knowledge and advice for clinicians on the potential advantages of volatile-induced myocardial protection, several authors have analyzed the available results in the form of meta-analyses. There are at least 5 meta-analyses on the subject [7–11]. Early meta-analyses performed by Yu *et al.* [9] and Symons *et al.* [11] contained studies assessing the myocardial protective effects and other non-cardiac postoperative outcomes in CABG patients who received either volatile anaesthesia or propofol. These analyses contained trials with a varied approach in pre- and post-conditioning volatile exposure and different volatile agents. Both studies indicated a small troponin reduction but recognized the need for higher quality trials. The third meta-analysis was limited to studies where desflurane and sevoflurane was compared with intravenous anaesthesia [8]. This study showed a 50% reduction in the incidence of myocardial infarction (MI), with a total of 69 MIs in 1,850 patients. The results of the meta-analysis should also be further scrutinized since the definition of post-cardiac surgery MI is neither universal nor specified in many of the reports included in the meta-analyses. This is problematic, in our view, given that troponin, which is usually central to the diagnosis of an MI, is universally released after cardiopulmonary bypass [13, 18, 28]. There was also a reduction in mortality based on a total of 16 deaths. We would contend that this event rate might be insufficient to lead to guidelines that may change clinical practice. The next meta-analysis, published in 2013, was based on the Bayesian approach and suggested that anaesthesia with volatile agents appeared to reduce mortality after cardiac surgery when compared with total intravenous anaesthesia [9]. Finally, Uhlig *et al.* [11] conducted large heterogeneous meta-analysis looking at the influence of volatile-based anaesthesia on mortality

in cardiac and non-cardiac patients. Among 4,890 cardiac patients, 2,587 received volatile anaesthesia. The authors showed that use of this approach was associated with a significant reduction in mortality. However, it should be noted that Uhlig *et al.* [13] looked at overall all-cause mortality analysed at all time points, which might suggest that volatiles might possess other organs' protective properties. On the other hand, they did not include any troponin data describing the degree of myocardial injury. Domanski *et al.* [14] have recently addressed this critically important issue of defining clinically important troponin release after cardiac surgery. In a meta-analysis of 7 trials in over 18,000 patients, clinically significant in-hospital events were only associated with troponin release of greater than 100 times the upper reference limit. Twenty percent of our population had troponin I in excess of 100 times the URL. Using this threshold, volatile anaesthesia was associated with a relative risk of a postoperative troponin value greater than 100 times the URL of 1.18 (95% CI 0.8–1.4) compared with the intravenous group.

SIGNIFICANCE

Our study is one of the first clinical investigations to examine the potential cardio-protective properties of combined volatile-induced anaesthesia and postoperative sedation as a pragmatic application of conditioning induced by anaesthetics. Our *post hoc* sample size allowed an 80% power to demonstrate a difference in troponin I levels between groups of at least 1.4 mcg/l. In addition, our sample size was sufficient to detect a categorical difference of 25% in the number of patients with troponin release in excess of 100 times the URL. Based on the results of our current study, and combined with the findings of several recent investigations [24–26], it appears that volatile-induced myocardial protection via combined anaesthesia and sedation may have a very limited impact on the clinical practice of cardiac anaesthesia and surgery. In this context, it should be mentioned that currently Landoni *et al.* [29] are conducting a large, multicentre, randomized multicenter trial aiming at the reduction of perioperative mortality in CABG patients. They have hypothesized that use of volatile-based anaesthesia will result in a reduction in mortality from 3 to 2%. The design of the study (MortalitY in caRdIAc surgery (MYRIAD): A randomizeD controlled trial of volatile anaesthetics) was recently published, and once finished, potentially will provide a definite answer to this question.

There are several reasons why volatile anaesthetics may not show a clinically significant effect. Firstly, animal studies are conducted on a genetically pure model [6, 30–34]. Cardiac surgical populations are more diverse [12, 23, 35–37]. In the original description of clinical ischaemic pre-conditioning, more than a third of the patients failed to show a protective response to ischaemia. Secondly, in several models of volatile-induced preconditioning, the authors have used high or repeated doses of volatile anaesthetic. We did not find this strategy readily feasible in patients; high doses (supra-anaesthetic doses) of volatile agents would lead to increased requirement for inotropic or vasopressor support, while intermittent doses may put patients at risk of intra-operative awareness.

Additionally, ischaemic preconditioning is blocked by sulfonylourea medications and high glucose levels, which block the cellular mechanisms responsible for protection [23, 30, 35, 38]. Patients in our study who were diabetics were not equally distributed in both groups, yet more patients suffering from diabetes mellitus were in the propofol group. Although more than one third of the patients in other studies were diabetic, most reports do not document the hypoglycaemic medications used, and thus the full extent of this effect cannot be estimated. Finally, several lines of evidence also support the hypothesis that propofol is cardio-protective, and thus the negative results may be due to a cardio-protective effect in the control arms of these trials and our study [39–41]. However, the dose of propofol which is required to provide cardio-protection is much higher than concentrations used in anaesthesia practice. Finally, it is possible that we were not able to detect differences between groups because we analysed patients with relatively good ventricular function and due to the fact of the consistent use (every 20 min.) of blood cardioplegia. Perhaps future studies should include sicker patients with multiple co-morbidities and less-preserved left ventricular function. Zaugg and Lucchinetti [42] recently discussed this topic extensively.

LIMITATIONS

Our study has several important limitations. Firstly, this study was not powered to detect a difference in clinically important outcomes, such as death. After completion of the study and the publication of a landmark investigation by Domanski *et al.* [14], we did power the study to detect a difference in the surrogate outcome of troponin release (*post hoc* analysis). Secondly, even though the optimal design of a clinical study includes randomization and double blinding, our investigation was designed as a single-evaluator blinded trial. Double blinding was not possible because of the type of intervention used. The AnaConDa® device must be connected to the endotracheal tube and requires the use of additional monitors and a syringe driver. In addition, to blind operating room and ICU personnel to propofol use, we would need to use an Intralipid infusion as a visually plausible placebo; Intralipid also possesses cardio-protective properties and is a free radical scavenger [43–45]. Thirdly, we analyzed 127 patients out of a total of 140 patients. Thirteen patients incurred serious perioperative complications

or withdrew consent, which precluded ongoing troponin assessment. Unfortunately, more patients from the volatile group had to be excluded than patients from the propofol group. This disproportion only partially could be explained by technical aspects of combined, volatile-based anaesthesia and postoperative sedation. Fourthly, although several preoperative characteristics were not equally distributed, this is not uncommon in smaller trials and accepted according to principles of biostatistics [46]. Fifthly, we had to use propofol for the induction of general anaesthesia. Although we are aware that this is not the most elegant way of separating 2 groups, unfortunately etomidate is not registered in Canada. We also elected not to use ketamine since it is not an ideal induction agent since it stimulates the sympathetic pathways and influence BIS monitoring. While it can be argued that propofol used for induction can have cardioprotective properties, given the dose used for induction purposes and rapid drug redistribution, the systemic concentration is unlikely to offer cardioprotective effects. Finally, the volatile doses used in this study could have potentially been insufficient to provide cardioprotection. Although previous studies have used much higher MAC concentrations, this would be unsafe for the haemodynamic management of complex cardiac surgical patients and does not reflect standard care in the operating room.

CONCLUSIONS

In summary, the results of our randomised and evaluator-blinded trial investigating the combined effects of volatile-based anaesthesia and postoperative sedation failed to demonstrate any advantageous effects on cardioprotection when compared with propofol-based anaesthesia and postoperative sedation in patients who underwent CABG and who had preserved left ventricular function. In both treatment groups (volatile vs. intravenous agent), troponin, haemodynamic, and inotropic and vasopressor, drug requirements were similar.

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Adres do korespondencji:
Marcin Wąsowicz
Department of Anesthesia and Pain Management
Toronto General Hospital
200 Elizabeth Street, Toronto ON M5G 2C4 Canada
e-mail: marcin.wasowicz@uhn.ca

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